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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	02/28/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 02/28/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/668,179	PALSSON ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-98* is/are pending in the application.

4a) Of the above claim(s) *40,42-45,53,55-58 and 64-98* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-39,41,46-52,54 and 59-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner. No drawings.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/24/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed November 22, 2006 has been entered.

The preliminary amendment filed September 24, 2003 has been entered. Claims 1-35 were canceled and Claims 36-98 were newly added.

Accordingly, Claims 36-98 remain pending in the instant application.

Applicants' election with traverse of Group I, Claims 36-63, is acknowledged. The elected invention is directed to a method for generating a tissue *in vivo* by culturing cells in a liquid culture medium and transferring the cultured cells to a patient to generate a tissue. Applicants further elected the species human bone marrow cells, from among the various cell types.

The restriction requirement is still deemed proper and is therefore made FINAL.

Claims 40, 42-45, 53, 55-58, and 64-98 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 22, 2006.

Claims 36-39, 41, 46-52, 54, and 59-63 are examined herein. The claims are examined herein only to the extent that they encompass the elected subject matter and further to the extent necessary to determine patentability of the generic claims.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, Application Nos. 08/857,594, 08/334,011, 07/815,513, 07/740,590, 07/737,024, 07/628,343, and 07/366,639, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

The earlier-filed applications upon which priority is claimed fail to provide adequate **support** under 35 U.S.C. 112 for Claims 36-39, 41, 46-52, 54, and 59-63 of this application, for the same reasons discussed hereinbelow as applied to the present application. The earlier-filed applications also fail to provide an **enabling disclosure** for the invention now being claimed in Claims 36-39, 41, 46-52, 54, and 59-63, for the same reasons discussed hereinbelow as a rejection under 35 U.S.C. 112, first paragraph, as applied to the instant application.

Thus, the earlier-filed applications do not meet the requirements under 35 U.S.C. 120 for the benefit of obtaining priority to an earlier-filed application.

Thus, the effective filing date for Claims 36-39, 41, 46-52, 54, and 59-63 is September 24, 2003, the filing date of the instant application.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple

assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 36-39, 41, 46-52, 54, and 59-63 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-7 of U.S. Patent No. 6,667,034. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims (Claims 1-7) are specifically directed to a method of bone marrow transplantation, wherein bone marrow tissue or blood is cultured in a liquid culture medium with either continuous or periodic replacement of the culture medium, at a rate of about 1 ml of medium per ml of culture per about 24 to 48 hour period. The cultured cells are then implanted into a recipient. The claims of the instant application are broader with respect to the type of tissue used as the starting material and broader with respect to the type of tissue generated in the recipient. Therefore, the instant claims read on the patented claims

directed to a method of bone marrow transplantation. Thus, the patented claims **anticipate** the claims of the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 36-39, 41, 46-52, 54, and 59-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The preliminary amendment filed September 24, 2003 asserts, at page 11, that "[s]upport for Claims 36-98 is found in Claims 1-35 and the specification on page 1, 2nd paragraph; page 2, 2nd paragraph; page 14, 6th paragraph; page 17, last paragraph; page 22; and page 47, last paragraph." The originally filed claims and the cited sections have been reviewed in their entirety and do not provide support for the newly added claims. In particular, there is no support for generating a tissue other than bone marrow, nor is there support for the range of "50 to 100%" daily replacement. The specification does not broadly contemplate generating any tissue, but rather only contemplates generating bone marrow and a method for bone marrow transplantation, particularly an improved method of bone marrow transplantation. Thus, the preliminary amendment does not point to any support for the newly added claims and the various new limitations recited therein.

As a first issue, the specification does not contemplate generating any tissue other than bone marrow tissue. The claims recite "generating a tissue" which covers everything from the simplest tissue

to the most complex tissue, including whole organs, such as a pancreas. However, the specification does not describe methods for generating complex tissues, like pancreatic tissue, brain tissue etc., and further does not describe methods for generating whole organs.

As a second issue, the limitation of "50 to 100% daily replacement" is not described in the as-filed specification. This range is not mentioned in the specification at all. On the contrary, the specification only contemplates the discrete values of 50% and 100% daily replacement of the culture media.

Thus, the claimed genus of generating a tissue, as broadly claimed, is not described in the specification.

To the extent that the claimed methods are not described in the specification, Claims 36-39, 41, 46-52, 54, and 59-63 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one of skill in the art how to practice a method that has not been described.

Enablement

Claims 36-39, 41, 46-52, 54, and 59-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a method of generating bone marrow tissue comprising

culturing a human cell composition comprising human stem and/or progenitor cells found in human bone marrow cells in a liquid culture medium which is replaced at a rate which is either (i) substantially continuous sufficient to obtain *ex vivo* human stem cell division and/or human progenitor cell expansion therein or (ii) equal to 50% daily replacement or 100% daily replacement thereby

providing *ex vivo* human stem cell division therein, while maintaining said culture under physiologically acceptable conditions; and

transferring the cultured human bone marrow cells into a patient to generated human bone marrow tissue *in vivo* in said patient,

does not reasonably provide enablement for the full scope of the claims, wherein any tissue is generated upon transplantation of human stem or progenitor cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

"generating a tissue" covers everything from the simplest tissue to the most complex tissue, maybe even a whole organ, like a pancreas.

The claims read on *de novo* generation of a tissue. Even where bone marrow tissue is generated upon the transplantation of cultured bone marrow cells, the tissue generated is a mixed tissue with cells from both the donor and recipient.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary (MPEP 2164.01(a)).

At the time the invention was made, successful implementation of cell therapy protocols was not routinely achievable by those skilled in the art. At the time the application was filed, the art of administering neuronal cells, to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable.

Rossi and Cattaneo (2002) acknowledge that "despite intense research activities and media attention, stem cell therapy for neurological disorders is still a distant goal" (abstract). The reference emphasizes the need for homogeneous populations of neural stem cells and the further need to understand the mechanisms required for "their proper integration into the injured brain" (abstract). The authors point out that "the functional integration of donor cells remains a highly demanding task that requires a profound understanding and control of the biological properties of both donor cells and the host environment" (page 401, column 2, paragraph 2, last sentence).

Cao et al. (2002) acknowledge the potential for the use of stem cells in therapeutic transplantation and for *in vivo* manipulation of endogenous precursors, but emphasize that "this at present is challenging and so far has been unsuccessful" (abstract and page 507, column 2, paragraph 2). The authors further point out that "[u]nderstanding mechanisms of NSC differentiation in the context of the injured CNS will be critical to achieving these therapeutic strategies" (abstract and page 507, column 2, paragraph 2).

Even under the best conditions, cell therapy in the central nervous system is highly unpredictable. For example, Milward et al. (1997) demonstrates that transplantation of neural stem cells (NSCs) to the CNS does not produce a therapeutic effect in a diseased animal. Milward et al. describes the transplantation of canine CNS NSCs into both rat and a shaking pup myelin mutant dog. In the rat, this resulted in the production of myelin by graft-derived cells. The authors report that the grafted cells integrated normally into the adult shaking pup cytoarchitecture. Yet despite all this, the clinical deficit of these animals was not ameliorated. Thus, it is clear that the production of myelin *in vivo* and normal integration of cells is not predictive of a therapeutic outcome. Given the unpredictability in the art of therapeutic transplantation, the development of therapeutic protocols requires substantial experimentation.

Mehler et al. (1999) disclose that many studies have suggested that the normal adult brain may lack the appropriate environmental signals to allow neural progenitors to realize their broad lineage potential. Specific neuropathologic conditions may alter the normal balance of regional environmental

signals, for example by releasing proinflammatory and other modulatory cytokines. The presence of these inappropriate cellular cues may predispose residual neural populations to undergo apoptosis. The authors state that "[t]his suggests that it may be necessary to promote lineage commitment of progenitor cells *in vitro* prior to transplantation into a damaged brain" (p. 782, column 1, paragraph 1).

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

No working examples demonstrate a therapeutic effect for the claimed method of cell therapy. The specification provides general teachings only, but does not provide specific guidance for treating the great variety of diseases covered by the claims. The claims cover a wide variety of routes of administration, but only bone marrow transplantation is specifically taught in the specification. The specification fails to provide specific guidance with regard to the site of injection and the extent of cellular persistence required and attainable in practice, to provide a therapeutic benefit for the treatment of any disease, other than those diseases already treated by bone marrow transplantation.

In view of the quantity of experimentation necessary to determine appropriate parameters for using the claimed method to achieve a therapeutic outcome, and given the lack of applicable working examples directed to the claimed method of generating a tissue, the limited guidance in the specification

with regard to transplantation protocols and their applicability to production of a specific therapeutic outcome, such as restored vision, the broad scope of the claims with regard to the wide variety of cell compositions that may be used, and further given the unpredictability in the art of therapeutic transplantation and cell therapy, undue experimentation would have been required for one skilled in the art to practice the claimed method of the invention in a human patient or other animals for therapeutic benefit.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-39, 41, 46-52, 54, and 59-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 36-39, 41, 46-52, 54, and 59-63 are indefinite in their recitation of "said patient" because there is no antecedent basis for this term. Appropriate correction is required.

Claims 36-39, 41, 46-52, 54, and 59-63 are indefinite in their recitation of "said cultured cells" because the term lacks antecedent basis. Thus, it is unclear which cultured cells are being referred to. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 36-39, 41, 46-52, 54, and 59-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al. (1991, Proc. Natl. Acad. Sci. 88: 6760-6764) and Liechty et al. (2000, Nature Medicine 6(11): 1282-1286).

Schwartz et al. (1991) disclose a method for culturing human bone marrow cells in liquid culture, wherein bone marrow cells are cultured in a liquid culture medium with either continuous or periodic replacement of the culture medium, at a rate of about 0.5 medium volume exchange per day. Increased culture perfusion at a rate of 3.5 volumes per week was found to be optimal for expanding stem cells.

Liechty et al. (2000) disclose a method for generating a variety of tissues from human mesenchymal stem cells, including chondrocytes, adipocytes, myocytes, cardiomyocytes, bone marrow stromal cells and thymic stroma. The reference also discloses that mesenchymal stem cells are multipotent cells present in adult bone marrow (abstract).

Since one of skill in the art would have wanted to obtain sufficient numbers of cells for transplantation, the skilled artisan would have used the culturing method disclosed by Schwartz et al. to expand a population of bone marrow cells for subsequent use in transplantation studies, such as those carried out by Liechty et al.

Therefore, the claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Conclusion

No claim is allowable.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER